

Conventional and Atypical Antipsychotics and the Risk of Hospitalization for Ventricular Arrhythmias or Cardiac Arrest

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Background: Conventional antipsychotic drugs have been implicated as a cause of ventricular arrhythmias and cardiac arrest, but no definitive information is available regarding atypical antipsychotics. We compared the effect of conventional and atypical antipsychotics on the risk of hospitalization for ventricular arrhythmias and cardiac arrest.

Methods: We conducted a case-control study on residents of nursing homes in 6 US states by using data from the Minimum Data Set linked to Medicare inpatient claims. Cases were residents hospitalized for ventricular arrhythmias or cardiac arrest between July 4, 1998, and December 30, 1999. For each case, we identified up to 5 controls residing in the same facility during the same period. The sample consisted of 649 cases and 2962 controls.

Results: Use of conventional antipsychotics was associated with a nearly 2-fold increase in risk of hospital-

ization for ventricular arrhythmias or cardiac arrest (adjusted odds ratio, 1.86; 95% confidence interval, 1.27-2.74). There was no increased risk associated with the use of atypical antipsychotics (odds ratio, 0.87; 95% confidence interval, 0.58-1.32). The risk of hospitalization for ventricular arrhythmias or cardiac arrest was highest among conventional users with cardiac disease (odds ratio, 3.27; 95% confidence interval, 1.95-5.47). However, cardiac disease and conventional antipsychotics did not show a synergistic effect (synergy index, 1.19).

Conclusions: Conventional but not atypical antipsychotics are associated with an increased risk of hospitalization for ventricular arrhythmias and cardiac arrest. The prescription of conventional antipsychotics in patients with cardiac disease should be carefully weighed.

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SOME ANTIPSYCHOTIC MEDICATIONS have been associated with an increased risk of ventricular arrhythmias, cardiac arrest, and sudden death.^{1,2} The literature includes several case series in schizophrenic patients treated with thioridazine hydrochloride,^{1,3} haloperidol,⁴ and other conventional antipsychotics.⁵ More recently, epidemiologic studies^{6,7} have confirmed a direct relationship between conventional antipsychotics and the risk of sudden death. In patients treated for schizophrenia this increased risk has been attributed to the QT-prolonging properties of conventional antipsychotics.^{8,9}

The newer, so-called atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine fumarate, ziprasidone hydrochloride, and aripiprazole) are more effective for the treatment of negative symptoms in schizophrenia and confer a lower risk of extrapyramidal side effects and tardive dyskinesia compared with con-

ventional agents.¹⁰ This better safety profile has expanded indications for treatment. Indeed, atypical antipsychotics are considered the mainstay of treatment for older persons with behavioral symptoms associated with dementia who reside in nursing homes.¹¹ Increasing use of atypical antipsychotics in diverse settings has been consistently documented.^{12,13}

Despite experimental evidence that some atypical antipsychotics can also prolong QT interval,⁵ only clozapine has been linked to serious cardiac problems.¹⁴ Risperidone has a minimal effect on QT interval,⁵ and the only reported case of sudden death was not due to ventricular arrhythmias.¹⁵ A single epidemiologic study on schizophrenic patients has suggested an increased risk of ventricular arrhythmias and cardiac arrest associated with risperidone, a finding not endorsed by the authors of that study.⁶

We conducted a case-control study to estimate the effect of conventional- and atypical-antipsychotic use on the risk of

hospitalization for ventricular arrhythmias or cardiac arrest among elderly residents of Medicare-Medicaid-certified nursing homes in 6 US states.

METHODS

DATA SOURCE

We used the Systematic Assessment of Geriatric Drug Use via Epidemiology database, which contains data from the Minimum Data Set (MDS). The MDS is a standardized, clinically based instrument used to assess residents in nursing homes across the United States. The MDS collects information on each resident's demographic, functional, medical, psychological, and cognitive status. The Centers for Medicare and Medicaid Services require that each certified facility conduct an MDS assessment of all residents on admission and quarterly thereafter. Since June 22, 1998, the Centers for Medicare and Medicaid Services maintain a centralized repository of all MDS data. The Systematic Assessment of Geriatric Drug Use via Epidemiology database has been described in detail elsewhere^{16,17} and has been proven a useful resource for epidemiologic research.¹⁸ Data collected in the nursing homes of 6 states (Illinois, Maine, Mississippi, New York, Ohio, and South Dakota) were used in this study.

CASE SELECTION

The Systematic Assessment of Geriatric Drug Use via Epidemiology database links MDS data to the Medicare inpatient claim files (part A). These files provide the admission diagnosis and up to 10 discharge diagnoses for any hospitalization, recorded by the *International Classification of Diseases, Ninth Revision (ICD-9)* codes.¹⁹ We identified cases by inpatient hospitalizations in which either the admission or the primary diagnosis was for cardiac arrest (*ICD-9 427.5*) or ventricular arrhythmias including paroxysmal ventricular tachycardia (*ICD-9 427.1*), ventricular flutter and fibrillation (*ICD-9 427.4*), ventricular flutter (*ICD-9 427.42*), and ventricular fibrillation (*ICD-9 427.41*). We used the first hospitalization to define case status among persons with multiple hospitalizations. Between July 4, 1998, and December 30, 1999, we identified 934 hospitalizations that met our case definition.

CONTROL SELECTION

We identified potential controls by inpatient hospitalizations in which the primary diagnosis at discharge was septicemia (*ICD-9 038-038.9*), gastrointestinal hemorrhage (*ICD-9 578, 578.0, 578.1, 578.9*), rectal bleeding (*ICD-9 569.3*), gastritis with bleeding (*ICD-9 535.1*), duodenitis with bleeding (*ICD-9 535.6*), or influenza (*ICD-9 487, 487.0, 487.1, 487.9*). We identified 18856 potential controls. To minimize the potential confounding effect of specific characteristics of the facilities,²⁰ each case was matched to a maximum of 5 controls residing within the same facility during the same period. We excluded cases for whom we could not identify at least 1 eligible control ($n=285$). The final sample consisted of 649 cases and 2962 controls. Cases included residents hospitalized for cardiac arrest (40.6%), paroxysmal ventricular tachycardia (34.5%), and ventricular flutter or fibrillation (24.9%).

ANTIPSYCHOTIC EXPOSURE

Nursing home staff recorded the name, dose, frequency, route of administration, whether the order was scheduled (standing

order) or as needed, and the National Drug Code for up to 18 drugs taken by the resident in the 7 days before the assessment.

We identified, for any study participant, the most proximal assessment reporting drug information before the hospitalization and defined it as the index assessment. We defined as exposed those residents for whom any antipsychotic use was reported at the index assessment. Exposed residents were (1) users of atypical antipsychotics including risperidone, olanzapine, quetiapine, and clozapine; (2) users of conventional agents including chlorpromazine, chlorprothixene, fluphenazine hydrochloride, haloperidol, loxapine, molindone hydrochloride, perphenazine, promazine hydrochloride, thioridazine hydrochloride, thiothixene, and trifluoperazine hydrochloride; and (3) users of both classes of antipsychotics. Unexposed residents were those for whom no antipsychotic use was reported at the index assessment.

POTENTIAL CONFOUNDERS

Sociodemographic characteristics including age, sex, and race or ethnicity, along with body mass index; indicators of functional, cognitive, and behavioral status; comorbid conditions; and concurrent drug use, were considered potential confounders.

To evaluate functional status, we used the Activities of Daily Living scale, a 7-item, 5-level score embedded in the MDS and based on the resident's performance in 7 areas: dressing, eating, toileting, bathing, locomotion, transferring, and incontinence.²¹ We classified the degree of dependence as mild (score of 0-1), moderate (score of 2-3), or severe (score of 4-5).

We used the Cognitive Performance Scale to measure residents' cognitive status. The Cognitive Performance Scale is a valid instrument and has excellent comparability with the Mini-Mental State Examination.²² The Cognitive Performance Scale score ranges from 0 (intact cognition) to 6 (severe dementia). We categorized cognitive impairment as follows: minimal (score of 0-1), moderate (score of 2-3), and severe (score of 4-6).

The degree of severity of behavioral problems was evaluated by an MDS-based index previously used in research²³ and considered appropriate in a recent consensus statement.²⁴ Residents were considered to have severe symptoms if they were verbally or physically abusive and socially inappropriate every day. Residents with moderate symptoms were those who were wandering, verbally or physically abusive, and socially inappropriate on occasions, but less than daily. If residents exhibited at least 1 of the previously mentioned symptoms but not all of them, or none of them, their condition was classified as mild or normal.

The MDS section on clinical diagnoses provided information about residents' comorbid conditions.¹⁷ These were recorded by physicians on the basis of medical history, hospital charts or record review, or physical examination when appropriate. We also considered concomitant medications with a known effect to prolong the QT interval and those with antiarrhythmic effect.

STATISTICAL ANALYSIS

We used conditional logistic regression models to quantify the effect of antipsychotic use on the likelihood of hospitalization for ventricular arrhythmias or cardiac arrest, simultaneously controlling for all potential confounders. Exposure categories in the first model included standing-order conventional-drug use, as-needed conventional-drug use, standing-order atypical-drug use, as-needed atypical-drug use, and use of both antipsychotic classes, with no antipsychotic use as the reference

Table 1. Principal Characteristics and Antipsychotic Use of Cases and Controls

Characteristic	% of Subjects	
	Cases (n = 649)	Controls (n = 2962)
Age group, y		
65-74	25.6	23.1
75-84	44.4	40.3
≥85	30.0	36.6
Female sex	57.6	66.5
Race/ethnicity		
White, not of Hispanic origin	82.0	82.2
Black, not of Hispanic origin	15.4	15.5
Hispanic	1.5	1.4
Other	1.1	0.9
BMI		
<18.5	14.6	15.8
18.5-24.9	45.9	48.3
25.0-29.9	25.0	23.7
≥30.0	14.5	12.2
Functional impairment (ADL score)		
Mild (0-1)	15.5	7.5
Moderate (2-3)	55.1	43.9
Severe (4-5)	29.4	48.6
Cognitive deficit (CPS score)		
Mild (0-1)	48.8	33.2
Moderate (2-3)	36.6	36.6
Severe (4-6)	14.5	30.1
Behavior index		
Normal/mild	83.5	80.0
Moderate	13.4	17.1
Severe	3.1	2.9
Cardiac arrhythmias	22.4	15.4
Heart failure	39.4	26.6
Coronary artery disease	23.4	17.5
Hypertension	53.9	50.9
Other heart disease	34.1	22.2
Chronic obstructive pulmonary disease	27.9	18.0
Hyperthyroidism	0.2	0.3
Diabetes mellitus	34.4	32.3
Alzheimer dementia	7.8	10.5
Dementia other than Alzheimer	24.1	30.4
Schizophrenia	2.5	2.5
Depression	26.6	28.7
Anxiety/bipolar disorder	11.8	10.5
Cancer	9.0	11.7
Antipsychotic use		
Atypical	5.7	8.2
Conventional	10.5	7.2
Both	0.8	0.4

Abbreviations: ADL, Activities of Daily Living; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CPS, Cognitive Performance Scale.

category. To estimate the effect of conventional relative to atypical antipsychotics, we used a second model including the same exposure categories with standing-order atypical-drug use as the reference category. We derived crude and adjusted odds ratios along with 95% confidence intervals from these models.

Since we hypothesized that preexisting cardiac disease could modify the effect of conventional antipsychotics on the risk of ventricular arrhythmias and cardiac arrest, we tested the interaction between any cardiac condition and conventional-antipsychotic use. We defined a resident as having a cardiac disease if at least 1 of the following diagnoses had been previously

documented: cardiac arrhythmias, heart failure, coronary artery disease, or other heart disease. According to Rothman and Greenland,²⁵ we combined cardiac disease and antipsychotic exposure into 1 variable with 12 levels. We included this variable in a conditional logistic regression model with “no antipsychotic use/no cardiac disease” as the reference category. We estimated the synergy index (SI), which measures interaction as a departure from additivity of the effects,²⁵ as follows:

$$SI = \frac{OR(AB) - 1}{[OR(A\bar{B}) - 1] + [OR(\bar{A}B) - 1]}$$

where *A* and *B* denote the presence of and \bar{A} and \bar{B} the absence of the 2 risk factors. In the absence of interaction between the two risk factors, the synergy index equals 1.

Statistical analysis was performed with SAS software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

Cases were younger and more likely to be male than were controls (**Table 1**). Residents in the control group were more likely to present a severe degree of functional impairment (48.6% vs 29.4%) and cognitive deficit (30.1% vs 14.5%). Cardiac diseases were more prevalent among cases, with a notable difference for heart failure (39.4% vs 26.6%). Instead, controls were more likely to be diagnosed as having Alzheimer disease (10.5% vs 7.8%) and other dementias (30.4% vs 24.1%). There was no difference in the prevalence of antipsychotic use between the 2 groups, but cases were more likely to use conventional agents (10.5% vs 7.2% among controls).

Table 2 shows that cases were more likely to be users of bronchodilators, antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, vasodilators, loop diuretics, calcium channel blockers, β -blockers, and coagulation modifiers.

Among atypical agents, risperidone was the most commonly used medication and accounted for more than 70% of prescriptions (**Table 3**). Use of other agents, quetiapine and clozapine in particular, was infrequent. For atypical antipsychotics, nearly 100% of prescriptions were standing orders. Haloperidol was the leading conventional antipsychotic (nearly 50% of prescriptions), followed by thioridazine. In this category, as-needed use varied from 25% for chlorpromazine and chlorprothixene to 0% in the case of thioridazine and several other agents.

After control for potential confounders, users of conventional antipsychotics showed an 86% increase in the risk of hospitalization for ventricular arrhythmias or cardiac arrest (odds ratio, 1.86; 95% confidence interval, 1.27-2.74) relative to nonusers (**Table 4**). There was no increased risk associated with the use of atypical antipsychotics (odds ratio, 0.87; 95% confidence interval, 0.58-1.32). We repeated the analysis including risperidone users as a separate exposure category, and we observed no effect on the risk of being hospitalized for ventricular arrhythmias or cardiac arrest by either risperidone alone or the other atypical antipsychotics.

Table 5 shows the combined effect of antipsychotic use and the presence of cardiac disease on the likelihood of experiencing the outcome. Among residents re-

Table 2. Concomitant Drug Use Among Cases and Controls

Drug	% of Subjects	
	Cases (n = 649)	Controls (n = 2962)
Lipid-lowering drugs	7.7	8.3
Systemic corticosteroids	10.0	10.4
Adrenergic bronchodilators	14.3	10.7
Theophylline derivatives	4.9	2.5
Antiarrhythmic drugs	42.1	29.8
ACE inhibitors	30.3	22.4
Central-acting antihypertensive drugs	3.1	4.8
Vasodilators	27.7	20.3
Thiazide diuretics	6.8	6.8
Loop diuretics	46.5	33.9
Potassium-sparing diuretics	4.9	3.8
Calcium channel blockers	23.9	19.7
β-Blockers	22.0	16.0
Inotropic agents	0.5	0.5
Oral antidiabetic agents	11.7	10.8
Coagulation modifiers	22.2	17.4
Gastrointestinal prokinetics	3.8	4.0
Antidepressants	29.0	28.7
Antibacterials	4.6	3.8
Antimycotics for systemic use	1.2	2.8
Opioids	1.5	1.0
Antihistamines	9.1	7.6
Other QT-prolonging drugs*	12.2	12.3

Abbreviation: ACE, angiotensin-converting enzyme.

*Includes amantadine hydrochloride, antimony sodium gluconate, arsenic trioxide, chloral hydrate, dexfenfluramine hydrochloride, famotidine, felbamate, fenoxedil, fosphenytoin sodium, mitoxantrone hydrochloride, octreotide, pentamidine, tacrolimus, tamoxifen citrate, terodiline hydrochloride, tizanidine hydrochloride, and vasopressin.

ceiving conventional antipsychotics, those with cardiac disease were 3.27 times (95% confidence interval, 1.95-5.47) and those with no cardiac disease were 2.05 times (95% confidence interval, 1.14-3.68) more likely to be hospitalized for ventricular arrhythmias and cardiac arrest, compared with nonusers without cardiac disease. The synergy index was 1.19, indicating no interaction between conventional-antipsychotic use and preexisting cardiac disease.

COMMENT

The results of this study document that the use of conventional antipsychotics is associated with an increased risk of hospitalization for ventricular arrhythmias and cardiac arrest. Our findings are consistent with those of Ray and colleagues,⁷ who reported a 2-fold increase in the rate of sudden death among patients aged 15 to 84 years receiving conventional antipsychotics compared with nonusers. In particular, these authors found that the sudden death rate ratio for current users of 100 mg or less of thioridazine hydrochloride or its equivalent, compared with nonusers, was 1.30, significantly less than that for moderate-dose users (rate ratio, 2.39). In the current analysis, we found an 86% increase in the risk of hospitalization for ventricular arrhythmias and cardiac arrest among conventional-antipsychotic users. The daily

Table 3. Drug Regimens Among Antipsychotic Users

Drug Name	No. of Subjects	Standing Orders, %	Daily Dose, mg	
			Mode	Range
Atypical Antipsychotic				
Clozapine	10	100.0	50.0	25.0-100.0
Olanzapine	64	100.0	2.5	2.5-15.0
Quetiapine fumarate	16	100.0	25.0	25.0-300.0
Risperidone	224	99.1	1.0	0.5-8.0
Conventional Antipsychotic				
Chlorpromazine	24	75.0	50.0	5.0-50.0
Chlorprothixene	4	75.0	NA	NA
Fluphenazine enanthate	13	100.0	2.0	2.0-5.0
Haloperidol	150	87.3	0.5	0.25-40.0
Loxapine	5	100.0	10.0	10.0-15.0
Molindone	5	100.0	10.0	5.0-10.0
hydrochloride				
Perphenazine	26	97.6	2.0	2.0-4.0
Promazine	27	77.8	NA	NA
hydrochloride				
Thioridazine	38	100.0	50.0	5.0-200.0
hydrochloride				
Thiothixene	6	100.0	5.0	5.0-10.0
Trifluoperazine	7	100.0	5.0	2.0-5.0
hydrochloride				

Abbreviation: NA, not applicable.

Table 4. Crude and Adjusted ORs and 95% CIs of Being Hospitalized for Ventricular Arrhythmias or Cardiac Arrest Among Residents Using Antipsychotics on a Standing Order*

Variable	Crude OR	Adjusted† OR	95% CI
Atypical vs no use	0.70	0.87	0.58-1.32
Conventional vs no use	1.53	1.86	1.27-2.74
Conventional vs atypical use	2.19	2.13	1.27-3.60

Abbreviations: CI, confidence interval; OR, odds ratio.

*Data for as-needed users are not shown.

†Adjusted for age, sex, race or ethnicity, body mass index, Activities of Daily Living score, Cognitive Performance Scale score, behavior index score, cardiac arrhythmias, heart failure, coronary artery disease, hypertension, other heart disease, chronic obstructive pulmonary disease, diabetes, Alzheimer disease, other dementias, schizophrenia, depression, anxiety, bipolar disorder, cancer, and concomitant drug use (including lipid-lowering drugs, systemic corticosteroids, adrenergic bronchodilators, theophylline derivatives, antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, central-acting antihypertensive drugs, vasodilators, thiazide diuretics, loop diuretics, potassium-sparing diuretics, calcium channel blockers, β-blockers, oral antidiabetic agents, coagulation modifiers, gastrointestinal prokinetics, antidepressants, antimycotics for systemic use, antihistamines, and other QT-prolonging drugs).

doses in our study were generally low (eg, thioridazine hydrochloride daily dose mode was 50 mg) and within the recommended range for this population.²⁴ Thus, our findings may indicate a particular sensitivity of the elderly population to the cardiotoxic effect of conventional antipsychotics.

In contrast, atypical antipsychotics did not appear to be associated with an increased risk of hospitalization for ventricular arrhythmias and cardiac arrest. Previous studies indicated that atypical antipsychotics do not affect QT

Table 5. Modification of Antipsychotic* Effect by Cardiac Disease on the Risk of Being Hospitalized for Ventricular Arrhythmias or Cardiac Arrest

Variable	Crude OR	Adjusted† OR	95% CI
Cardiac disease and atypical use	1.54	1.54	0.88-2.70
Cardiac disease and conventional use	3.33	3.27	1.95-5.47
No cardiac disease and atypical use	0.91	0.98	0.52-1.85
No cardiac disease and conventional use	1.85	2.05	1.14-3.68
Cardiac disease and no use	2.29	1.86	1.45-2.39
No cardiac disease and no use	1.00	1.00	

Abbreviations: CI, confidence interval; OR, odds ratio.

*Results in the table refer to users of antipsychotics on a standing order. Data for as-needed users are not shown.

†Adjusted for the same factors as in Table 4.

interval when used at therapeutic doses.²⁶⁻²⁹ However, new evidence suggests that there could be important dose-related differences in the effect on QT interval.^{30,31} High doses of risperidone (mean dose, 7.2 mg) have been associated with a mean QT increase of 4.4 milliseconds in a double-blind comparison with olanzapine.³⁰ Sporadic cases of risperidone overdose associated with severe QT prolongation have been described,^{32,33} but a review of the overdose profiles indicated that atypical antipsychotics are generally safe.³⁴

Cardiac disease may be a predisposing factor for ventricular arrhythmias and cardiac arrest. We found consistently that the presence of a cardiac disease was a strong confounder in the relationship under study. However, the use of conventional antipsychotics and the presence of a cardiac disease did not show a synergistic effect on the risk of hospitalization for ventricular arrhythmias and cardiac arrest, pointing to the absence of a biological interaction.

Our study has several strengths. In times when atypical antipsychotics are rapidly replacing conventional antipsychotics^{12,13} and indications for the use of these drugs are expanding,¹¹ this study provides new information on a still unresolved clinical question. A possible cardiovascular risk associated with atypical antipsychotics is a critical issue especially in view of the suspiciously high rates of venous thromboembolism³⁵ and ischemic stroke reported among patients receiving these medications.³⁶ Finally, given the nature of the outcome, no clinical trials investigating this issue would be deemed ethical and observational studies are invaluable.

This study also has some limitations. Since we used claims for outcome identification, we missed all cases of ventricular arrhythmias and cardiac arrest resulting in death before hospital referral. The use of claims data to assess the outcome may raise concerns of lack of accuracy and potential for misclassification. Nonetheless, cardiac events such as ventricular arrhythmias and cardiac arrest require electrocardiographic confirmation, and this may lower the potential for inaccuracy. In our database there is no available information on QT-interval measurements. However, QT interval is more a marker of risk

than a mechanism of arrhythmia, prolongation does not necessarily result in ventricular arrhythmias, and there is no established safety threshold.^{37,38} Atypical-antipsychotic use has been associated with body weight increase and dyslipidemia.³⁹ Because of the limited duration of the study, we could not assess the possible impact of these risk factors on the outcome. Finally, no information was available on other potential confounders such as electrolyte disturbances, heart rate variability,⁴⁰ and other predisposing conditions.⁴¹

In conclusion, this study has documented that conventional but not atypical antipsychotics are associated with an increased risk of hospitalization for ventricular arrhythmias and cardiac arrest. An increased risk is present even for doses within the recommended range. Thus, physicians should use these drugs cautiously among elderly patients, especially those with cardiac disease. We have documented an increased relative risk of an event that is exceedingly rare. Therefore, the clinical relevance of the estimated effect size at the population level should be judged by taking into account the low background rate of the event. Moreover, atypical antipsychotics are not more efficacious than conventional agents,⁴² nor is there sufficient evidence to claim an overall superior cardiac side effect profile of atypical antipsychotics compared with conventional agents. In fact, the use of these agents may be challenged by newer adverse effects: substantial weight gain and elevated cholesterol and insulin levels, which might in turn affect cardiac health.⁴³ Thus, therapeutic choice should be based on a careful evaluation of the patient's individual needs and risk profile, along with the beneficial and harmful effects of both classes of antipsychotics.

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REFERENCES

1. Straus SM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the risk of sudden cardiac death. *Arch Intern Med.* 2004;164:1293-1297.
2. Shader RI, Greenblatt DJ. Potassium, antipsychotic agents, arrhythmias, and sudden death. *J Clin Psychopharmacol.* 1998;18:427-428.
3. Giles TD, Modlin RK. Death associated with ventricular arrhythmia and thioridazine hydrochloride. *JAMA.* 1968;205:108-110.
4. Jackson T, Ditmanson L, Phibbs B. Torsade de pointes and low-dose oral haloperidol. *Arch Intern Med.* 1997;157:2013-2015.
5. Taylor DM. Antipsychotics and QT prolongation. *Acta Psychiatr Scand.* 2003;107:85-95.
6. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *BMJ.* 2002;325:1070-1074.
7. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry.* 2001;58:1161-1167.
8. Studenik C, Lemmens-Gruber R, Heistracher P. Proarrhythmic effects of antidepressants and neuroleptic drugs on isolated, spontaneously beating guinea-pig Purkinje fibers. *Eur J Pharm Sci.* 1999;7:113-118.

9. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet*. 2000;355:1048-1052.
10. Kapur S, Remington G. Atypical antipsychotics. *BMJ*. 2000;321:1360-1361.
11. American Geriatrics Society and American Association for Geriatric Psychiatry. Consensus statement on improving the quality of mental health care in US nursing homes: management of depression and behavioral symptoms associated with dementia. *J Am Geriatr Soc*. 2003;51:1287-1298.
12. Hermann RC, Yang D, Ettner SL, Marcus SC, Yoon C, Abraham M. Prescription of antipsychotic drugs by office-based physicians in the United States, 1989-1997. *Psychiatr Serv*. 2002;53:425-430.
13. Liperoti R, Mor V, Lapane KL, Pedone C, Gambassi G, Bernabei R. The use of atypical antipsychotics in nursing homes. *J Clin Psychiatry*. 2003;64:1106-1112.
14. Modai I, Hirschmann S, Rava A, et al. Sudden death in patients receiving clozapine treatment: a preliminary investigation. *J Clin Psychopharmacol*. 2000;20:325-327.
15. Ravin DS, Levenson JW. Fatal cardiac event following initiation of risperidone therapy. *Ann Pharmacother*. 1997;31:867-870.
16. Bernabei R, Gambassi G, Lapane KL, et al. Characteristics of the SAGE database: a new resource for research on outcomes in long-term care: SAGE (Systematic Assessment of Geriatric drug use via Epidemiology) Study Group. *J Gerontol A Biol Sci Med Sci*. 1999;54:M25-M33.
17. Gambassi G, Landi F, Peng L, et al. Validity of diagnostic and drug data in standardized nursing home assessments: potential for geriatric pharmacoepidemiology. *Med Care*. 1998;36:167-179.
18. Gambassi G, Lapane KL, Sgadari A, et al. Effects of angiotensin-converting enzyme inhibitors and digoxin on health outcomes of very old patients with heart failure. *Arch Intern Med*. 2000;160:53-60.
19. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977.
20. Intrator O, Castle NG, Mor V. Facility characteristics associated with hospitalization of nursing home residents: results of a national study. *Med Care*. 1999;37:228-237.
21. Katz S, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-919.
22. Morris JN, Fries BE, Mehr DR, et al. MDS cognitive performance scale. *J Gerontol*. 1994;49:M174-M182.
23. Gambassi G, Lapane KL, Sgadari A, Landi F, Mor V, Bernabei R. Measuring health outcomes for older people using the SAGE database. *Can J Aging*. 2000;19 (suppl 2):67-86.
24. Snowden M, Sato K, Roy-Byrne P. Assessment and treatment of nursing home residents with depression or behavioral symptoms associated with dementia: a review of the literature. *J Am Geriatr Soc*. 2003;51:1305-1317.
25. Rothman KJ, Greenland S. Concepts of interaction. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology*. 2nd ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1998:329-342.
26. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsades de pointes, and sudden death. *Am J Psychiatry*. 2001;158:1774-1778.
27. Kang UG, Kwon JS, Ahn YM, et al. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry*. 2000;61:441-446.
28. Bosch RF, Baumbach A, Bitzer M, Erley CM. Intoxication with olanzapine. *Am J Psychiatry*. 2000;157:304-305.
29. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG; Seroquel Study Group. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry*. 1997;54:549-557.
30. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol*. 1997;17:407-418.
31. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2001;158:765-774.
32. Moore NC, Shukla P. Risperidone overdose. *Am J Psychiatry*. 1997;154:289-290.
33. Kopala LC, Day C, Dillman B, Gardner D. A case of risperidone overdose in early schizophrenia: a review of potential complications. *J Psychiatry Neurosci*. 1998;23:305-308.
34. Capel MM, Clobridge MG, Henry JA. Overdose profiles of new antipsychotic agents. *Int J Neuropsychopharmacol*. 2000;3:51-54.
35. Hägg S, Spigset O. Antipsychotic-induced venous thromboembolism: a review of the evidence. *CNS Drugs*. 2002;16:765-776.
36. Committee on Safety of Medicines. Latest news: March 9, 2004: Atypical antipsychotic drugs and stroke. Available at: <http://www.mca.gov.uk/aboutagency/regframework/csm/csmhome.htm>. Accessed April 28, 2004.
37. Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy*. 2003;23:881-908.
38. Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA*. 2003;289:2120-2127.
39. Nasrallah H. A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology*. 2003;28(suppl 1):83-96.
40. Agelink MW, Majewski T, Wurthmann C, et al. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine. *J Clin Psychopharmacol*. 2001;21:8-13.
41. Coulter DM, Bate A, Meyboom RH, Lindquist M, Edwards IR. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ*. 2001;322:1207-1209.
42. Lee PE, Gill SS, Freedman M, et al. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ*. 2004;329:75.
43. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. *Drugs*. 2004;64:701-723.